International Journal of Therapeutic Applications, Volume 1, 2012, 32 - 37

POTENTIAL ROLE OF ANTIOXIDANTS IN CANCER MANAGEMENT

Sajal Kumar Jha[1], Roopa Karki[2], Amitava Ghosh[3]
[1, 3] **Bengal College of Pharmaceutical Sciences & Research, Durgapur, West Bengal.**
[2] **Acharya & B.M Reddy College of Pharmacy, Bangalore, Karnataka.**

ABSTRACT

Cancer has a complex etiology with multiple risk factors that involve the interplay between genetic and environmental influences. Epidemiological studies show that a high intake of antioxidant-rich foods is inversely related to cancer risk. Among a number of mechanistic hypotheses, diet-derived antioxidants have been proposed to contribute to explain these findings. Antioxidants protect against oncogenic transformation by radiation and free radical–producing anticancer drugs in experimental systems. Antioxidants do reduce the painful side effects of radiation and chemotherapy, thus supporting the beneficial effects of antioxidants in protecting normal cells during treatment and acting as adjuvants in the treatment of certain cancers. The effect of antioxidants on tumor cell growth, differentiation and apoptosis have been studied in cell culture models, transplanted tumors in syngeneic animals and in athymic mice, and in patients with certain tumors. These studies have revealed that vitamins, when used individually, can induce apoptosis selectively in cancer cells within certain dose ranges, or can inhibit or stimulate the growth of cancer cells, depending on the dose. Antioxidants nutrients such as vitamin E, vitamin C, vitamin A, and Beta-carotene are involved in detoxification of the Reactive oxygen species. Vitamin E, A, and Beta-carotene are lipophilic antioxidants whereas vitamin C is hydrophilic antioxidant. Vitamin E function as a free radical chain breaker particularly it interferes with the propagation step of lipid peroxidation. The vitamin A and Beta-carotene have actions by quenching both singlet oxygen and other free radicals generated by photochemical reactions.

Key Words: Cancer; antioxidants, chemotherapy, vitamins; nutrients; free radicals.

INTRODUCTION

Treatment of malignant diseases with drugs is a rather recent development- started after 1940 when nitrogen mustard was used, but progress has been rapid, both in revealing pathobiology of the diseases and in discovery of new drugs. In addition, attempts have been made to define optimal combinations, treatment strategies and patient support measures [1].There are many different chemotherapeutic agents used in cancer treatment. Most of the chemotherapeutic drugs can be divided into alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, and other antitumour agents. All of these drugs affect cell division or DNA synthesis and function in some way. Several classes of chemotherapy work by producing a reactive oxygen compound or free radical. Cancer survivors receive a wide range of advice from many sources about foods they should eat, foods they should avoid, how they should exercise, and what types of supplements or herbal remedies they should take. Antioxidant show promise in cancer

therapy by their palliative action, reducing painful side effects associated with treatment. In several *in*

vitro and animal studies the hypothesis has been tested that antioxidants benefit patients receiving chemotherapy. The main function of antioxidants is to Prevent oxidation in various contexts. It has been known for some time that antioxidants Play a very important biological role in the body by protecting against oxidative damage (particularly oxidative damage to DNA), thus preventing cardiovascular, neurological and carcinogenic diseases and delaying chronic health problems like cataracts.

The Food and Drug Administration (FDA) defines antioxidants only as dietary supplements to be taken in addition to normal food consumption in an effort to prevent these diseases.In principle two opposing mechanistic arguments could be advanced supporting or refuting this notion. On the one hand, antioxidants might protect cancer cells against the oxidative damage induced by chemotherapy, which

would mitigate against their use. On the other hand they may enhance drug-induced cytotoxicity by blocking reactive oxidant species [2].

CANCER CHEMOTHERAPY:

The ultimate clinical effectiveness of any anti-cancer drug requires that it kill malignant tumor cells *in vivo* at doses that allow enough cells in the patient's critical tissues (e.g., bone marrow, gastrointestinal tract) to survive so that recovery can occur. This is difficult to accomplish because, in general, anticancer drugs are most useful against malignant tumor with a high proportion of dividing cells, and some normal tissues such as the bone marrow and G1 tract also have a high cell-proliferation rate. Chemotherapy agents can be divided into several categories: alkylating agents (e.g., cyclophosphamide, ifosfamide), antibiotics which affect nucleic acids (e.g., doxorubicin, bleomycin), platinum compounds (e.g., cisplatin), mitotic inhibitors (e.g., vincristine), antimetabolites (e.g., 5-fluorouracil), camptothecin derivatives (e.g., topotecan), biological response modifiers (e.g., interferon), and hormone therapies (e.g., tamoxifen). The agents most noted for creating cellular damage by initiating free radical oxidants are the alkylating agents, the tumor antibiotics, and the platinum compounds[3].

DEBATE ON ANTIOXIDANTS IN CANCER CARE:

Most oncologists do not recommend antioxidants to their patients during radiation therapy, chemotherapy, or experimental therapy. Some may recommend a multiple-vitamin preparation containing low doses of antioxidants after the completion of therapy. This recommendation may be harmful because like normal cells, cancer cells need certain amounts of micronutrients including antioxidants for growth and survival. Indeed, low doses of individual dietary antioxidants may also stimulate the proliferation of some cancer cells. Therefore; it is likely that recommendation of low doses of multiple vitamins containing low doses of micronutrients including antioxidants after therapy may increase the risk of recurrence of the primary tumor among those who are in remission.

Antioxidants nutrients such as vitamin E, vitamin C, vitamin A, and Beta-carotene are involved in detoxification of the Reactive oxygen species (ROS). Vitamin E, A, and Beta-carotene are lipophilic antioxidants whereas vitamin C is hydrophilic antioxidant. Vitamin E function as a free radical chain breaker particularly it interferes with the propagation step of lipid peroxidation. The vitamin A and Beta-carotene have actions by quenching both singlet oxygen and other free radicals generated by photochemical reactions.

Simone II et al. (2007) wrote a review which showed that since the 1970s, 280 peer-reviewed *in vitro* and *in vivo* studies, including 50 human studies involving 8,521 patients, 5,081 of whom were given nutrients, have consistently shown that those non-prescription antioxidants and other nutrients do not interfere in therapeutic modalities of cancer. Furthermore, they enhance the killing of therapeutic modalities of cancer, decrease their side effects, and protect normal tissue. For them in 15 human studies, 3,738 patients who took non-prescription antioxidants and other nutrients actually had increased survival [2].

Antioxidants nutrients in cancer treatment:

Vitamin A:

The effectiveness of vitamin A depends on the type and amount that was used. It has been shown to inhibit the growth of some cancers. At high doses, variable extents of tumor size reduction have been reported. Vitamin A, however, has been shown to have very little or no effect on several human tumors, which include melanoma, non-small cell lung carcinoma, prostate cancer, and breast cancer. Some of the variants of vitamin A have been shown to produce extreme toxicity, especially when used in higher doses. Most researchers in this area agree that the use of single antioxidant vitamins, which require very high doses for its effectiveness, has no value in the treatment of cancer [4].

Vitamin C:

Vitamin C (ascorbate) has been the most researched and applied nutrient in cancer. Vitamin C has been shown to inhibit the growth of cancer cells in both animal and human studies. There are other studies which show that vitamin C at lower doses can actually stimulate the growth of cancer cells. Linus Pauling has shown that the use of 10 gms of sodium ascorbate can prolong and improve the quality of life in cancer patients [5]. Medical studies are now showing us that calcium ascorbates are

actually safer and more effective in patients with cancer

Vitamin E:

There have been several studies that have shown that vitamin E used in supplementation will inhibit the growth and increase the cell death of various cancers. Research studies are showing that d alpha-tocopherol succinate is the most potent form of vitamin E in inhibiting the growth of cancer cells and causing increased cell death of these cancer cells. The higher antioxidant and biological effect of this natural form of vitamin E has also been demonstrated in several different studies[2].

Carotenoids:

There are over 1000 different carotenoids. However, the most common ones are beta carotene, lycopene, and lutein. Most of the studies have been done using these carotenoids. They have been shown to inhibit the growth of cancer cells and, in the case of leukoplakia (a precancerous tumor), a dramatic reversal was shown. Lycopene has been shown to decrease the risk of prostate cancer. Beta-carotene has also been shown to decrease the damage to normal cells by radiation therapy. It is felt that a combination of carotenoids is the best recommendation for patients with cancer[4].

B. Vitamins:

There have not been any studies showing major benefits with the B vitamins and cancer treatment. Vitamin B3 may enhance the radiation response of some tumors. However, all in all most of the studies show that supplementation with a single vitamin could actually be harmful[2].

Selenium:

The trace mineral selenium is not itself an antioxidant, but within cells it is incorporated into selenoproteins, some of which have antioxidant functions (i.e. glutathione peroxidase). In addition, selenium may directly induce tumor cell apoptosis and inhibit cancer cell spread in the tissues.It is a potent modulator of eukaryotic cell growth with strictly concentration dependant effects. The protective effect of this mineral is especially associated with its presence in glutathione peroxidase and thioredoxin reductase, enzymes that protect the DNA and other cellular components against oxidative damage caused by reactive oxygen species[6].

Flavonoids:

Flavonoids and their polymers constitute a large class of food constituents, synthesized by plants, many of which alter metabolic processes and have a positive impact on health. Flavonoids are a subclass of polyphenols. Polyphenols are abundant micronutrients in our diet, and evidence for their role in the prevention of degenerative diseases such as cancer and cardiovascular diseases is emerging. The capacity of flavonoids to act as antioxidants *in vitro* has been the subject of several studies in the past years, and important structure–activity relationships of the antioxidant

activity have been established. The antioxidant efficacy of flavonoids *in vivo* is less documented, presumably because of the limited knowledge on their uptake in humans[7].

Melatonin:

Unlike the classical antioxidants, melatonin is devoid of prooxidative activity and all known intermediates generated by the interaction of melatonin with reactive species are also free radical scavengers. This phenomenon is defined as the free radical scavenging cascade reaction of the melatonin family. Due to this cascade, one melatonin molecule has the potential to scavenge up to 4 or more reactive species. This makes melatonin very effective as an antioxidant. Physiologic and pharmacologic concentrations of the pineal hormone melatonin have shown chemopreventive, oncostatic, and tumor inhibitory effects in a variety of in vitro and in vivo experimental models of neoplasia. The tissue protective actions of melatonin are attributed to its antioxidant activity though, under certain conditions, melatonin might also exert oxidant effects, particularly in cancer cells[8].

Dexrazoxane:

Dexrazoxane received FDA approval in 1995 for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer. Doxorubicin was administered intravenously as a bolus infusion. Dexrazoxane was administered intravenously 30 min prior to each dose of doxorubicin in the 10:1 ratio dexrazoxane: doxorubicin. Dexrazoxane reduces the incidence and severity of early and late cardiotoxicity in children with solid tumors receiving doxorubicin chemotherapy. Administration of dexrazoxane was

well tolerated and no second malignant neoplasm was observed during the follow-up period, which might be contributed by the limited follow-up period [8].

Glutathione:

The results of the neurophysiologic examinations performed before and immediately after chemotherapy suggest that combined glutathione/cisplatin therapy is safe and effective in the treatment of ovarian cancer, and has extremely low peripheral neurotoxicity[2].

EFFECTIVENESS MIXTURE OF ANTIOXIDANTS

Individual antioxidant vitamins produce varying degrees of tumor regression in vivo only at very high doses which frequently cause toxicity, especially with retinoid derivatives. At lower doses, they may be ineffective or stimulate the growth of cancer cells. Therefore, the use of single vitamins in cancer treatment has no biological or clinical merit. This led to the investigation of the effects of multiple antioxidants on the growth of cancer cells in vitro in order to demonstrate whether the individual vitamins can interact with each other to produce a higher degree of growth inhibition selectively on cancer cells than can be achieved by single vitamins at the same doses[9]. The use of individual antioxidants in cancer patients produces varying results and only at very high levels, which in the case of some may cause significant toxicity. The lower doses of single antioxidants have been shown to actually increase tumor growth. However, when nutrients, they were able to demonstrate a marked inhibition of cancer cell growth. These antioxidants were given at levels that if used alone would produce no results or even enhance the cancer growth. When individual antioxidants were increased within the mixture, there was further reduction of the cancer.

ANTIOXIDANTS IN COMBINATION WITH STANDARD CANCER THERAPIES:

Most of the studies that have been performed with single antioxidants both in the lab and within the body have shown an enhancement of the chemotherapeutic medications. However, there is an occasional study which has shown a negative effect when a single antioxidant is used with a particular chemotherapeutic drug, i.e. synthetic beta-carotene and 5-FU. When these same antioxidants are used in combination with several other antioxidants, there is only enhancement of the effectiveness of the drugs. Most oncologists and radiation therapists remain skeptical of using antioxidant vitamins with their patients who are receiving standard cancer therapies. Since both the chemotherapeutic drugs and radiation use the production of excessive free radicals to destroy or inhibit the growth of the tumor, they are worried that the cancer cells will be more resistant to their treatments. However, except for a rare situation where only a single antioxidant is used, this does not hold true when you examine the medical studies that are available. In fact, just the opposite occurs. Those cancer patients receiving standard cancer therapies who are also taking a combination of antioxidant vitamins and their supporting nutrients actually have significantly better results than those patients who simply take the standard therapies. Recently, Cisplatin has been combined with selenium, as this nutrient has been found to protect against nephrotoxicity[10]. The incorporation of doxorubicin (0.1 µg/ml) and vitamin E as alpha-tocopheryl succinate (10 µg/ml) separately did not affect the cell multiplication of Hela cells. However, when both agents were combined, cell multiplication was inhibited by 80% [11]. In other words, the effect of a mixture of antioxidants in combination with tumor therapeutic agents will greatly enhance the survival rates of these patients.

ANTIOXIDANTS IN TOXICITY REDUCTIONS

Normal cells are actually protected from the toxic effects of these standard cancer treatments because normal cells will not take excessive amounts of antioxidants. They will, however, be able to build up their natural antioxidant defense systems so that they are performing at optimal levels. Here are just a few of the positive benefits found in the medical literature:

1. Vitamin Ereducesbleomycin-lung fibrosis, adriamycin-induced cardiac toxicity, and skin necrosis. Vitamin E also has been shown to protect normal cells from radiation damage.
2. Coenzyme Q10 has also been shown to protect against adriamycin-induced cardiac toxicity.
3. Beta-carotene reduces the adverse effects of radiation and some chemotherapeutic drugs.

excessive free radicals they produce, it only makes common sense that cancer patients using

nutritional supplements would tolerate these medications better and recover from their Since most of the side effects caused by the standard cancer therapies are caused by the treatments quicker.

CONCLUSION:

The potential importance of the antioxidant network in cancer prevention is a relatively new topic of research. Numerous epidemiological studies have shown that a diet high in a wide, varied range of antioxidants is protective against the development of malignancies. Most integrative protocols recognize that the use of antioxidants will likely be more beneficial if used in the context of a well rounded dietary and supplement program. Antioxidants and other essential nutrients affect the neoplastic process by exerting various mechanisms in addition to their antioxidant activity. They show anti-proliferative effects, act as anti-metastatic and anti-angiogenic agents, and promote apoptosis in cancer cells. They also provide immediate relief to the patient by reducing the toxicity of chemotherapy.The use of antioxidants during chemo/radiation therapy is very controversial. Although it's generally recommended that antioxidants not be given concurrently with chemo/radiation therapy, the literature, which is complex and clearly inconclusive, is not necessarily supportive of this position. Their use can be recommended, however, when chemo/radiation therapy is not being given. There are some antioxidants, specifically high dose melatonin, where clinical studies do support concurrent use with chemo/radiation therapy. A prudent approach to the use of antioxidants would be to withhold them when there is potential for significant benefit from chemo/radiation therapy. In more advanced situations, where there is increased Reactive Oxygen Species production, and the patient is likely depleted of antioxidants, and when the chemo/radiation therapy is likely to be less efficacious, consideration should be given to including antioxidants (in conjunction with a multiagent integrative protocol), particularly as adverse treatment reactions might be minimized.

Antioxidants and other nutrients can work synergistically with conventional chemotherapy agents in cancer patients. The apprehension that higher doses of antioxidants are toxic to the body is not validated. Well-designed, large-scale clinical studies in cancer patients using the Cellular Medicine approach need to be conducted so that information about the benefits of this approach can be convincingly extended to concerned physicians and, through them, to cancer patients around the world.

REFERENCES:

1. Tripathi, K. D., 2008. Anticancer Drugs. 6th Edition; Jaypee Brother Medical Publishers(P) Ltd., pp 819-820.

2. Lamson, D.W.&Brignall, M.S., 1999. Antioxidants in cancer therapy; their actions andinteractions with oncologic therapies, Alter Med Rev 4(5): 304-29.

3. Gurtoo, H.L., Bansal, S.K., Pavelic Z. & Struck, R.F. 1985. Effects of the induction of hepatic microsomal metabolism on the toxicity of cyclophosphamide, *Br J Cancer* 51: 67-75.

4. Meyskens, F.L., Jr., Liu, P.Y., Tuthill, R.J., Sondak, V.K., Fletcher, W.S., Jewell, W.R. Samlowski, W., Balcerzak, S.P., Rector, D.J. & Noyes, R.D. 1994. Randomized trial of vitamin A versus observation as adjuvant therapy in high-risk primary malignant melanoma: a Southwest Oncology Group study, J Clin Oncol 12: 2060-2065.

5. Cameron, E. & Pauling, L. 1976. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer, Proc Natl Acad Sci U S A 73(10): 3685-3689.

6. Combs, G.F. Jr. 2005. Current Evidence and Research Needs to Support a Health Claim for Selenium and Cancer Prevention, J Nutr 135(2): 343-347.

7. Beecher, G.R. 2003. Overview of dietary flavonoids: nomenclature, occurrence and intake, J Nutr 133(10):3248S-3254S.

8. Tan, D-x., Manchester, L.C., Hardeland, R., Lopez-Burillo, S., Mayo, J.C., Sainz, R.M. & Reiter, R.J. 2003. Melatonin: a hormone, a tissue factor, an autocoid, a paracoid, and an antioxidant vitamin, Journal of Pineal Research 34(1): 75–78.

9. Prasad KN, Hernandez C, Edwards-Prasad J, Nelson J, Borus T, Robinson WA. 1994.

Modification of the effect of tamoxifen, cis-platin, DTIC and interferon-a2b on human melanoma cells in culture by a mixture of vitamins. Nutr Cancer 22:233–245.

10. Blasiak J, Kowalik J, Trzeciak A, Wojewodzka M. 1999. Cytotoxicity and DNA repair in human lymphocytes exposed to three anticancer platinum drugs. Neoplasma 46: 61-63.

11. Prasad KN. Antioxidants in cancer care: When and how to use them as an adjunct to standard and experimental therapies. Expert Rev Anticancer Ther 2003; 3:903-915.